REMARKS

Status of the Claims

Claims 1-4, 6, 7, 9-15, 17, 18, 20-22 and 33-36 were pending in the application.

Claims 20-22 were withdrawn as directed to a non-elected invention.

Claims 1-4, 6, 7, 9-15, 17, 18 and 33-36 were rejected.

By way of this amendment, claims 20-22 have been canceled and claims 40-45 have been added.

Upon entry of this amendment, claims 1-4, 6, 7, 9-15, 17, 18, 33-36 and 40-45 will be pending.

Summary of the Amendment

Claims 20-22 have been canceled without prejudice.

New claims 40, 41 and 45 are dependent on claims 1, 12, and 33, respectively, and limit the immunogen to a viral antigen. Support for the new claims is found throughout the specification. No new matter has been added.

New claims 42-44 correspond to claims 20-22 but are dependent on elected embodiments. Support for the new claims is found throughout the specification. No new matter has been added.

Rejections under 35 U.S.C. § 112

Claims 1-4, 6-7, 9-15, 17-18, and 33-36 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is asserted that the specification does not enable the use of DR5 as an "immunomodulatory protein." Applicants respectfully disagree.

Applicants respectfully assert that the present invention as claimed is enabled for one of ordinary skill in the art because contrary to the Office's allegation, the present

specification provides clear and specific guidance so that a person of ordinary skill in the art would not have to practice undue experimentation to make and/or use the present invention. Applicants contend that the Office has failed to meet its burden of providing sufficient reasoning and evidence to conclude that one skilled in the art would doubt the objective truth of Applicants assertion of enablement. The Office relies upon several references showing DR5's ability to induce apoptosis as evidence that it is not an immunomodulatory protein. None of these references even discuss whether or not DR5 is an immunomodulatory protein. An issue has been raised about the existence of decoys as evidence that one skilled in the art would not accept the assertion that that DR5 is an immunomodulatory protein. In view of all of the evidence of record, Applicants assert the office has failed to meet its burden and should conclude that the claimed invention is enabled.

Moreover, provided herewith is a Declaration by co-inventor Dr. David B. Weiner which includes data in the form of a manuscript. The data in the manuscript show that DR5 acts as a immunomodulatory protein in that its presence enhances the immune response against the immunogen encoded by a nucleotide sequence of a nucleic acid molecule delivered with the DR5-encoding sequences. The data show a clear enhancement of immune response.

Although the invention is not intended to be bound by any particular theory, the manuscript includes a possible explanation as to why the apoptosis inducing protein DR5 can enhance immune responses in vaccines. According to a possible theory of how the invention works, which included in the discussion section of the manuscript, muscle cells take up the nucleic acid sequences that encode DR5 and the immunogen. When expressed in muscle cells the expression of DR5 in the muscle cells results in the muscle cell undergoing apoptosis which leads to apoptotic fragments that get taken up by Dendretic cells which leads to an enhanced immune response relative similar vaccines which lack DR5. Regardless of this theory, the data in the manuscript show an improved immune response against the immunogen.

When the evidence of record is considered in its totality, one skilled in the art would conclude that Applicants' specification provided an enabling disclosure to make and use the claimed invention. The data in the specification specifically address the Examiner's skepticism about whether DR5 has immunomodulatory activity. It clearly does.

Accordingly, one of skill in the art would conclude that the present invention is enabled because the skilled artisan has to do nothing more than follow the procedures in Applicants' specification to make and/or use the claimed invention.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

Rejections under 35 U.S.C. §102

Claims 1-3, 6, and 12 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent No. 6,417,328 (hereinafter the "'328 patent"). The Office alleges that the '328 patent teaches all the limitations of the claims as written and therefore, anticipates the claimed invention. Applicants respectfully disagree.

First, the rejection is improper because the Office has asserted that sterile as used in the '328 Patent means the same thing pyrogen free, or at least sterile compositions as described in the '328 Patent are necessarily pyrogen free. This is not true. Claims 1 and 12 recite, in part, "A pyrogen-free composition comprising a plasmid..." or "A pyrogen-free composition comprising two plasmids..." The '328 patent does not discuss or even suggest a pyrogen-free composition comprising a plasmid or two plasmids as described in the claims. Therefore, the '328 patent does not teach every element of the pending claims and fails to anticipate the present invention. The Office's position is that the sterile compositions described in columns 22-23 are pyrogen free. This contradicts evidence of record in the form of U.S. Patent No. 5,693,622 (the "'622" Patent) which was applied in the rejection under 35 U.S.C. § 103(a). The '622 Patent discloses preparation of plasmid DNA for delivery to vertebrates and describes the purified patent as sterile and pyrogen free, indicating that the two are different and

distinct. They are in fact different and distinct. Something can be sterile and not be pyrogen free.

Next, the Office has used a description of clinical preparations to describe the condition of certain plasmids which were disclosed in a description of experiments done to study the mechanism of DR5 activity in cells. The plasmids in the '328 Patent which correspond to the plasmids in the claims were not intended for pharmaceutical use and therefore would not have been prepared according to the '328 Patent's description of preparation of pharmaceutical material. It is the Office's position that the '328 Patent discloses plasmids that include coding sequences for DR5 and an immunogen (column 27, lines 14-23) and that the '328 Patent discloses making pharmaceutical compositions suitable for injection (columns 22-23). Therefore, the Office concludes, the teachings of preparation of sterile compositions set forth in columns 22 and 23 apply to the plasmids that include coding sequences for DR5 and an immunogen set forth on column 27. The Office further concludes sterile compositions described in columns 22-23 are pyrogen free. These conclusions lead the Office to conclude that the claims are anticipated.

Applicants wish to point out that it is well settled that the reference must be read in their entirety. The subject matter being claimed must be compared to what the references actually disclose to one skilled in the art. Applicants urge that a fair and proper reading of the '328 Patent does not support a finding the reference anticipates the claims. Applicants also wish to point out that while plasmids that include coding sequences for DR5 and an immunogen are disclosed in the '328 Patent, Applicants do not concede that the '328 Patent does not disclose compositions comprising two plasmids in which one encodes DR5 and one encodes an immunogen.

More importantly however, Applicants urge that while plasmids that include coding sequences for DR5 and an immunogen are disclosed (column 27, lines 14-23) and compositions that comprise two plasmids in which one encodes a flagged fusion protein that include DR5 sequence and one encodes a flagged fusion protein with FLAME sequences, they are disclosed in the context of experiments performed to study DR5's apoptosis inducing activity in specifically described experiments. There is no suggestion

that such plasmids or compositions would be used in the clinical uses suggested in columns 22-23. The clinical uses disclosed in the specification are for the use of DR5 as a therapeutic agent. The DR5 is delivered by means of delivery of a plasmid that encodes DR5 but there is no suggestion anywhere of co-delivering a nucleotide sequence that encodes an immunogen. There is no teaching or suggestion anywhere of using DR5 in combination with immunogens in any clinical application. Rather, any clinical uses of DR5 disclose its use as a stand alone agent. The disclosure referring to preparing the plasmids to be sterile for injection do not apply to the plasmids disclosing in columns 27 and 28. The constructs and compositions disclosed in columns 27 and 28 were not for clinical use but rather for experiments which were performed on cells and which were designed to study mechanisms of action, not as clinical agents.

Applicants do not agree with the examiner's assertion that sterile as disclosed in columns 22 and 23 means pyrogen free but such an argument is not even the most relevant inquiry. The references must be read in their entirety and applied based upon what they disclose to one skilled in the art. The '328 Patent does not disclose plasmids and compositions which comprise nucleotide sequence that encodes an immunogen prepared for injection. Thus, even if the '328 Patent discloses pyrogen free plasmids and compositions based upon the disclosure on columns 22 and 23, such disclosure does not include plasmids and compositions which comprise nucleotide sequence that encodes an immunogen prepared for injection.

When the references are read in their entirety and applied based upon what they disclose to one skilled in the art, the reference does not support the rejection under 35 U.S.C. §102(e). One having ordinary skill in the art would not conclude that the '328 Patent discloses the claimed invention. In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 102 be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1-3, 6, and 12 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the '328 patent in view of U.S. Patent No. 5,693,622 (the "'622" Patent). It is asserted that in view of the combination of teachings of '328 Patent, which

teaches to prepare sterile pharmaceutical composition comprising a plasmid encoding DR5 for administration to a mammal, and the teachings of the '622 Patent, which discloses standard methodologies for preparing DNA for administration to vertebrates in sterile, pyrogen free solutions, it would be prima facie obvious to one skilled in the art to use the methods disclosed in the '622 Patent to prepare plasmids that encode DR5 and an immunogen as taught by '328 Patent. Applicants respectfully disagree and respectfully urge that the rejection has been improperly formulated.

The '328 Patent teaches to prepare sterile pharmaceutical composition comprising a plasmid encoding DR5 for administration to a mammal. It does not disclose preparing sterile pharmaceutical composition comprising a plasmid or combination of plasmids encoding DR5 and an immunogen for administration to a mammal. As discussed above, the disclosure in the '328 Patent related to plasmids encoding DR5 and an immunogen had nothing to do the preparation of a sterile pharmaceutical composition for administration to a mammal.

The '622 Patent discloses methodologies for preparing DNA for administration to vertebrates in sterile, pyrogen free solutions.

The combination of teachings yields the use of methods disclosed in the '622 Patent to prepare plasmids that encode DR5 as taught by '328 Patent for use in pharmaceuticals. The combination of teachings does not yield the use of methods disclosed in the '622 Patent to prepare plasmids that encode DR5 and immunogens as taught by '328 Patent for use in experiments to study the mechanism of action of DR5 in cells.

Applicants respectfully urge that nothing in the combination of references teaches or suggests pyrogen free compositions that comprise a plasmid or plasmids that encode DR5 and immunogens. Nothing in the combination of references teaches or suggests using plasmid or plasmids that encode DR5 and immunogens as pharmaceuticals so their was no motivation to purify the compositions to be pyrogen free.

When the references are read in their entirety, it is clear that the '328 Patent discloses sterile pharmaceutical compositions that comprise plasmids that encode DR5

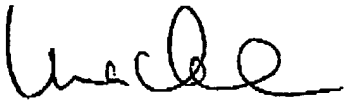
but that there is no disclosure of sterile pharmaceutical compositions that comprise plasmid or plasmids that encode DR5 and immunogens. Thus, when combined with the '622 Patent, it may be possible to argue that combined teachings would yield sterile, pyrogen free pharmaceutical compositions that comprise plasmids that encode DR5. However, the combination does not yield sterile, pyrogen free pharmaceutical compositions that comprise plasmid or plasmids that encode DR5 and immunogens. There is no teaching or suggestion to purify the compositions that comprise plasmid or plasmids that encode DR5 and immunogens disclosed in the '328 Patent to the level of purity needed for injectable pharmaceuticals.

One having ordinary skill in the art would not conclude that the combination of the teachings of the '328 Patent with those of the '622 would render the invention prima facie obvious. In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

Conclusion

The claims are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicants invite the Examiner to contact the undersigned at (215) 665-5592 to clarify any unresolved issues raised by this response.

Respectfully submitted,



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